加味青娥丸治疗膝骨关节炎的作用机制研究

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摘　要　目的:探讨加味青娥丸治疗膝骨关节炎(knee osteoarthritis,KOA)的作用机制。**方法:**将符合要求的 120 例 KOA 患者随机分为加味青娥丸组和芍药丸组,每组 60 例;分别口服加味青娥丸和芍药丸,每次 1 丸,每天 3 次,连续服用 12 周。服药期间 2 组患者均进行患肢皮肤牵引及不负重功能锻炼。当患者关节疼痛不能缓解或加重,无法忍受时,给予塞来昔布胶囊,每次 1 粒,每天 1 次,疼痛控制后立即停止服用塞来昔布胶囊。分别于治疗前和治疗 12 周后测定 2 组患者的膝关节疼痛视觉模拟评分(visual analogue score,VAS)和西安大略和麦克马斯特大学(Western Ontario and McMaster Universities,WOMAC)骨关节炎指数评分,并测定患者血清白细胞介素 -1β(interleukin -1β,IL -1β)、肿瘤坏死因子 α(tumor necrosis factor -α,TNF -α)和一氧化氮(nitric oxide,NO)水平,以及外周血单核细胞(peripheral blood mononuclear cell,PBMC)基质金属蛋白酶 -3 mRNA(matrix metalloproteinase -3 mRNA,MMP -3 mRNA)表达水平。**结果:**①膝关节疼痛 VAS 评分及 WOMAC 评分。治疗前 2 组患者膝关节疼痛 VAS 评分及 WOMAC 评分比较,组间差异均无统计学意义($t=0.626$,$P=0.553$;$t=0.856$,$P=0.394$);治疗 12 周后芍药丸组膝关节疼痛 VAS 评分及 WOMAC 评分均高于加味青娥丸组($t=9.075$,$P=0.000$;$t=17.149$,$P=0.000$)。治疗 12 周后加味青娥丸组膝关节疼痛 VAS 评分及 WOMAC 评分均较治疗前降低($t=10.392$,$P=0.000$;$t=19.075$,$P=0.000$);芍药丸组膝关节疼痛 VAS 评分及 WOMAC 评分治疗前后比较,差异均无统计学意义($t=0.664$,$P=0.508$;$t=1.860$,$P=0.065$)。②血清 IL -1β 水平。治疗前 2 组各级别患者血清 IL -1β 水平比较,差异无统计学意义($F=0.612$,$P=0.894$)。治疗 12 周后加味青娥丸组患者血清 IL -1β 水平与治疗前相比,差异有统计学意义($F=16.986$,$P=0.000$);Ⅰ、Ⅱ级患者血清 IL -1β 水平较治疗前降低($P=0.000$;$P=0.000$),Ⅲ、Ⅳ级患者血清 IL -1β 水平与治疗前相比,差异均无统计学意义($P=0.075$;$P=0.161$)。治疗 12 周后芍药丸组各级别患者血清 IL -1β 水平与治疗前相比,差异无统计学意义($F=0.651$,$P=0.885$)。治疗 12 周后 2 组患者血清 IL -1β 水平比较,差异有统计学意义($F=3.881$,$P=0.044$);加味青娥丸组Ⅰ、Ⅱ级患者血清 IL -1β 水平均低于芍药丸组($P=0.008$;$P=0.000$);2 组Ⅲ、Ⅳ级患者血清 IL -1β 水平比较,组间差异无统计学意义($P=0.342$;$P=0.444$)。③血清 TNF -α 水平。治疗前 2 组各级别患者血清 TNF -α 水平比较,差异无统计学意义($F=1.447$,$P=0.695$)。治疗 12 周后加味青娥丸组患者血清 TNF -α 水平与治疗前相比,差异有统计学意义($F=103.189$,$P=0.000$);Ⅰ、Ⅱ级患者血清 TNF -α 水平较治疗前降低($P=0.000$;$P=0.000$),Ⅲ、Ⅳ级患者血清 TNF -α 水平与治疗前相比,差异均无统计学意义($P=0.281$;$P=0.079$)。治疗 12 周后芍药丸组各级别患者血清 TNF -α 水平与治疗前相比,差异无统计学意义($F=1.065$,$P=0.786$)。治疗 12 周后 2 组患者血清 TNF -α 水平比较,差异有统计学意义($F=13.958$,$P=0.003$);加味青娥丸组Ⅰ、Ⅱ、Ⅳ级患者血清 TNF -α 水平均低于芍药丸组($P=0.000$;$P=0.000$;$P=0.018$);2 组Ⅲ级患者血清 TNF -α 水平比较,差异无统计学意义($P=0.125$)。④血清 NO 水平。治疗前 2 组各级别患者血清 NO 水平比较,差异无统计学意义($F=0.505$,$P=0.918$)。治疗 12 周后加味青娥丸组患者血清 NO 水平与治疗前相比,差异有统计学意义($F=25.740$,$P=0.000$);Ⅰ、Ⅱ级患者血清 NO 水平较治疗前降低($P=0.000$;$P=0.000$),Ⅲ、Ⅳ级患者血清 NO 水平与治疗前相比,差异均无统计学意义($P=0.080$;$P=0.121$)。治疗 12 周后芍药丸组各级别患者血清 NO 水平与治疗前相比,差异无统计学意义($F=0.427$,$P=0.935$)。治疗 12 周后 2 组患者血清 NO 水平比较,差异有统计学意义($F=5.621$,$P=0.039$);加味青娥丸组Ⅰ、Ⅱ级患者血清 NO 水平均低于芍药丸组($P=0.000$;$P=0.000$);2 组Ⅲ、Ⅳ级患者血清 NO 水平比较,组间差异无统计学意义($P=0.062$;$P=0.226$)。⑤PBMC MMP -3 mRNA 水平。治疗前及治疗 12 周后,2 组各级别患者 PBMC MMP -3 mRNA 水平比较,组间差异均无统计学意义($F=0.002$,$P=0.999$;$F=0.033$,$P=0.998$)。治疗 12 周后加味青娥丸组和芍药丸组各级别患者 MMP -3 mRNA 水平与治疗前相比,差异均无统计学意义($F=0.029$,$P=0.999$;$F=0.002$,$P=0.999$)。**结论:**加味青娥丸治疗早中期 KOA 的机理之一可能是通过各种途径下调血清 IL -1β、TNF -α 及 NO 水平,从而抑制软骨细胞凋亡和软骨基质降解。

关键词　骨关节炎,膝;青娥丸;白细胞介素 1β;肿瘤坏死因子 α;一氧化氮;基质金属蛋白酶 -3;治疗,临床研究性

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Study on the mechanism of action of Jiawei Qing'e Wan(加味青娥丸) for the treatment of knee osteoarthritis

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ABSTRACT **Objective**: To explore the mechanism of action of Jiawei Qing'e Wan(加味青娥丸, JWQEW) for the treatment of knee osteoarthritis(KOA). **Methods**: One hundred and twenty patients with KOA were randomly divided into two groups, 60 cases in each group. The patients were treated with JWQEW and Shaoyao Wan(芍药丸, SYW) respectively, one pill 3 times a day for consecutive 12 weeks. All cases received skin traction and non-weight-bearing functional exercise in affected limbs during the treatment, and those patients who suffered from unrelieved or aggravated knee pain were given Celecoxib capsules, 1 pill once a day. Celecoxib capsules would be withdrew as long as the knee pain was controlled. The knee pain visual analogue score(VAS) and Western Ontario and McMaster Universities(WOMAC) osteoarthritis index scores were evaluated before the treatment and after 12 - week treatment respectively. The serum level of IL - 1β, TNF - α and NO and the expression of PBMC MMP - 3 mRNA were also detected at the same time. **Results**: There were no statistical differences in knee pain VAS scores and WOMAC scores between the two groups before the treatment($t = 0.626$, $P = 0.553$; $t = 0.856$, $P = 0.394$). After 12-week treatment, the knee VAS scores and WOMAC scores were higher in SYW group compared to JWQEW group($t = 9.075$, $P = 0.000$; $t = 17.149$, $P = 0.000$). After 12-week treatment, the knee VAS scores and WOMAC scores decreased in JWQEW group ($t = 10.392$, $P = 0.000$; $t = 19.075$, $P = 0.000$). There were no statistical differences between pretreatment and post-treatment in knee VAS scores and WOMAC scores in SYW group($t = 0.664$, $P = 0.508$; $t = 1.860$, $P = 0.065$). There was no statistical difference in the serum level of IL - 1β between the 2 groups before the treatment($F = 0.612$, $P = 0.894$). After 12-week treatment, there was statistical difference in the serum level of IL - 1β in JWQEW group between pretreatment and post-treatment($F = 16.986$, $P = 0.000$). The serum level of IL - 1β decreased after the treatment in grade Ⅰ and Ⅱ cases($P = 0.000$, $P = 0.000$), while there was no statistical difference in serum level of IL - 1β between pretreatment and post-treatment in grade Ⅲ and Ⅳ cases($P = 0.075$, $P = 0.161$). After 12-week treatment, there was no statistical difference in the serum level of IL - 1β in SYW group between pretreatment and post-treatment($F = 0.651$, $P = 0.885$). There was statistical difference in the serum level of IL - 1β between the 2 groups after the treatment($F = 3.881$, $P = 0.044$). The serum IL - 1β level was lower in JWQEW group compared to SYW Group in grade Ⅰ and Ⅱ cases($P = 0.008$, $P = 0.000$), while there was no statistical difference in the serum IL - 1β level in grade Ⅲ and Ⅳ cases between the 2 groups($P = 0.342$, $P = 0.444$). There was no statistical difference in the serum level of TNF - α between the 2 groups before the treatment($F = 1.447$, $P = 0.695$). After 12 - week treatment, there was statistical difference in the serum level of TNF - α in JWQEW group between pretreatment and post-treatment($F = 103.189$, $P = 0.000$). The serum level of TNF - α decreased in grade Ⅰ and Ⅱ cases after the treatment($P = 0.000$; $P = 0.000$), while no statistical difference was found in grade Ⅲ and Ⅳ cases($P = 0.281$, $P = 0.079$). After 12-week treatment, there was no statistical difference in the serum level of TNF - α in SYW group between pretreatment and post - treatment($F = 1.065$, $P = 0.786$) and there was statistical difference between the two groups ($F = 13.958$, $P = 0.003$). The serum level of TNF - α was lower in grade Ⅰ, Ⅱ, and Ⅳ cases in JWQEW group compared to SYW group ($P = 0.000$, $P = 0.000$, $P = 0.018$), while there was no statistical difference in grade Ⅲ cases between the 2 groups($P = 0.125$). There was no statistical difference in the serum level of NO between the 2 groups before the treatment($F = 0.505$, $P = 0.918$). There was statistical difference in the serum level of NO in JWQEW group between pretreatment and post-treatment($F = 25.740$, $P = 0.000$). The serum level of NO decreased in grade Ⅰ and Ⅱ cases after the treatment($P = 0.000$, $P = 0.000$), while there was no statistical difference between pretreatment and post-treatment in grade Ⅲ and Ⅳ cases($P = 0.080$, $P = 0.121$). After 12-weeks treatment, there was no statistical difference between pretreatment and post-treatment in serum NO level in all grades of cases in SYW group($F = 0.427$, $P = 0.935$). There was significant difference in the serum level of NO between the two groups after 12-week treatment($F = 5.621$, $P = 0.039$). The serum level of NO was lower in grade Ⅰ and Ⅱ cases in JWQEW group compared to SYW group($P = 0.000$, $P = 0.000$), while there was no statistical difference in grade Ⅲ and Ⅳ cases between the 2 groups($P = 0.062$, $P = 0.226$). There was no statistical difference in the expression level of PBMC MMP - 3 mRNA between the two groups before the treatment and after 12-week treatment($F = 0.002$, $P = 0.999$; $F = 0.033$, $P = 0.998$). There was no statistical difference in the expression level of PBMC MMP - 3 mRNA between pretreatment and post-treatment in both of the two groups($F = 0.029$, $P = 0.999$; $F = 0.002$, $P = 0.999$). **Conclusion**: By down-regulating the serum levels of IL - 1β, TNF - α and NO through various pathways, JWQEW can inhibit cartilage cell apoptosis and cartilage matrix degradation, which may be one of the mechanisms of action for treatment of early-middle KOA.

Key words osteoarthritis, knee; Qinge pill; interleukin - 1beta; tumor necrosis factor - alpha; nitric oxide; matrix metalloproteinase 3; therapies, investigational

近年来膝骨关节炎（knee osteoarthritis，KOA）的防治已成为医学界研究的热点问题，但其病因病机尚不清楚。Heppner 等[1]的研究发现，在 KOA 模型软骨中，细胞外基质的丢失与软骨细胞的调亡数量相关。进一步的研究发现，KOA 患者软骨中凋亡的软骨细胞数量明显增高，而且其凋亡数量与 KOA 的严重程度成正相关[2-3]。

大多数 KOA 患者最为严重的临床症状为疼痛和功能障碍，而目前 KOA 的治疗也主要以减轻疼痛、改善患肢功能、提高生命质量、延缓病情发展为主。中药复方制剂治疗 KOA 具有价格低廉、疗效可靠、不良反应少的优势。本研究对加味青娥丸治疗 KOA 的作用机制进行了初步探讨，现总结报告如下。

1　临床资料

1.1　一般资料　纳入研究的患者共 120 例，均为 2013 年 6 月至 2014 年 6 月在华中科技大学同济医学院附属协和医院治疗的患者，男 48 例，女 72 例；年龄（56.1 ± 6.2）岁；病程（26.3 ± 4.8）个月；单侧病变者 91 例，其中左侧 41 例、右侧 50 例，双侧病变者 29 例。按 Kellgren - Lawrence 分级标准[4]，Ⅰ级 40 例、Ⅱ级 36 例、Ⅲ级 26 例、Ⅳ级 18 例。试验方案经医院伦理委员会审核通过。

1.2　诊断标准　采用美国风湿病学会制定的 KOA 诊断标准[5-6]。

1.3　纳入标准　①符合上述诊断标准；②同意参与本项临床试验，签署知情同意书。

1.4　排除标准　①因骨髓炎、骨肿瘤及骨结核引起的 KOA 患者；②合并其他影响膝关节的疾病者，如银屑病、梅毒性神经病、褐黄病、代谢性骨病、急性创伤等；③近 3 个月内进行过膝关节腔内药物注射、关节腔冲洗、关节镜手术或近 1 个月内使用过激素者。

2　方　法

2.1　病例分组　采用随机数字表将纳入研究的 120 例患者随机分为加味青娥丸组和芍药丸组，每组 60 例。2 组患者基线资料比较，差异无统计学意义，有可比性（表 1）。

表 1　2 组 KOA 患者基线资料比较

组别	例数	性别（例）		年龄（$\bar{x} \pm s$，岁）	病程（$\bar{x} \pm s$，月）	病变部位（例）			Kellgren - Lawrence 分级（例）			
		男	女			左膝	右膝	双膝	Ⅰ级	Ⅱ级	Ⅲ级	Ⅳ级
加味青娥丸组	60	23	37	55.2 ± 5.6	25.6 ± 4.1	22	24	14	19	19	14	8
芍药丸组	60	25	35	57.1 ± 6.8	27.1 ± 5.4	19	26	15	21	17	12	10
检验统计量		$\chi^2 = 0.139$		$t = 1.671$	$t = 1.714$	$\chi^2 = 0.334$			$\chi^2 = 0.587$			
P 值		0.709		0.097	0.089	0.846			0.899			

2.2　临床治疗　加味青娥丸组和芍药丸组分别口服加味青娥丸和芍药丸，每次 1 丸，每天 3 次，连续服用 12 周。服药期间 2 组患者均进行患肢皮肤牵引及不负重功能锻炼。当患者关节疼痛不能缓解或加重，无法忍受时，给予塞来昔布胶囊（辉瑞制药有限公司，国药准字 J20120063，规格 0.2 g），每次 1 粒，每天 1 次，当疼痛控制后立即停止服用塞来昔布胶囊。加味青娥丸的药物组成包括：盐杜仲 480 g、盐补骨脂 240 g、炒核桃仁 150 g、丹参 240 g、大蒜 120 g、丹参 240 g，制作时将大蒜蒸熟，干燥后与杜仲、丹参、补骨脂打粉，核桃仁捣碎，将所有药物混匀、过筛，每 100 g 粉末加炼蜜 50 ~ 70 g 制成大蜜丸[7]。芍药丸成分为芍药，每 100 g 芍药粉加炼蜜 50 ~ 70 g 制成与加味青娥丸大小相似的大蜜丸。

2.3　试验指标测定　分别于治疗前和治疗 12 周后测定 2 组患者的膝关节疼痛视觉模拟评分（visual analogue score，VAS）和西安大略和麦克马斯特大学（Western Ontario and McMaster Universities，WOMAC）骨关节炎指数评分[8]，并空腹抽取肘正中静脉血测定患者血清白细胞介素 - 1β（interleukin - 1β，IL - 1β）、肿瘤坏死因子 α（tumor necrosis factor - α，TNF - α）和一氧化氮（nitric oxide，NO）水平，以及外周血单核细胞（peripheral blood mononuclear cell，PBMC）基质金属蛋白酶 - 3 mRNA（matrix metalloproteinase - 3mRNA，MMP - 3 mRNA）表达水平。血清 IL - 1β、TNF - α、NO 水平采用酶联免疫吸附法测定，PBMC MMP - 3 mRNA 表达水平采用聚合酶链式反应技术测定[9]。

2.4　数据统计分析　采用 SPSS13.0 软件进行数据统计分析，2 组患者性别、病变部位及 Kellgren - Lawrence 分级的组间比较采用 χ^2 检验，年龄、病程、膝关节疼痛 VAS 评分、WOMAC 评分的组间比较采用 t 检验，血清 IL - 1β、TNF - α、NO 水平及 PBMC MMP - 3 mRNA 表达水平的比较采用随机区组设计的方差分析，进一步

两两比较采用 LSD-t 检验,检验水准 $\alpha = 0.05$。

3　结　果

3.1　膝关节疼痛 VAS 评分及 WOMAC 评分　治疗前 2 组患者膝关节疼痛 VAS 评分及 WOMAC 评分比较,组间差异均无统计学意义;治疗 12 周后芍药丸组膝关节疼痛 VAS 评分及 WOMAC 评分均高于加味青娥丸组。治疗 12 周后加味青娥丸组膝关节疼痛 VAS 评分及 WOMAC 评分均较治疗前降低;芍药丸组膝关节疼痛 VAS 评分及 WOMAC 评分治疗前后比较,差异均无统计学意义。见表 2、表 3。

表 2　2 组 KOA 患者治疗前后膝关节疼痛 VAS 评分比较　$\bar{x} \pm s$,分

组别	例数	膝关节疼痛 VAS 评分		t 值	P 值
		治疗前	治疗 12 周后		
加味青娥丸组	60	4.6 ± 1.8	1.9 ± 0.9	10.392	0.000
芍药丸组	60	4.4 ± 1.7	4.2 ± 1.6	0.664	0.508
t 值		0.626	9.075		
P 值		0.553	0.000		

表 3　2 组 KOA 患者治疗前后 WOMAC 指数评分比较　$\bar{x} \pm s$,分

组别	例数	WOMAC 指数评分		t 值	P 值
		治疗前	治疗 12 周后		
加味青娥丸组	60	53.8 ± 9.4	26.6 ± 5.8	19.075	0.000
芍药丸组	60	52.3 ± 9.8	49.2 ± 8.4	1.860	0.065
t 值		0.856	17.149		
P 值		0.394	0.000		

3.2　血清 IL-1β 水平　治疗前 2 组各级别患者血清 IL-1β 水平比较,差异无统计学意义($F = 0.612$,$P = 0.894$)。治疗 12 周后加味青娥丸组患者血清 IL-1β水平与治疗前相比,差异有统计学意义($F = 16.986$,$P = 0.000$);Ⅰ、Ⅱ级患者血清 IL-1β 水平较治疗前降低($P = 0.000$;$P = 0.000$),Ⅲ、Ⅳ级患者血清 IL-1β 水平与治疗前相比,差异均无统计学意义($P = 0.075$;$P = 0.161$)。治疗 12 周后芍药丸组各级别患者血清 IL-1β 水平与治疗前相比,差异无统计学意义($F = 0.651$,$P = 0.885$)。治疗 12 周后 2 组患者血清 IL-1β 水平比较,差异有统计学意义($F = 3.881$,$P = 0.044$);加味青娥丸组Ⅰ、Ⅱ级患者血清 IL-1β 水平均低于芍药丸组($P = 0.008$;$P = 0.000$);2 组Ⅲ、Ⅳ级患者血清 IL-1β 水平比较,组间差异无统计学意义($P = 0.342$;$P = 0.444$)。见表 4。

表 4　2 组 KOA 患者血清 IL-1β 水平比较　$\bar{x} \pm s$,pg · mL^{-1}

病情分级[1)]	加味青娥丸组			芍药丸组		
	例数	治疗前	治疗 12 周后	例数	治疗前	治疗 12 周后
Ⅰ级	19	333 ± 58	289 ± 45	21	341 ± 63	337 ± 61
Ⅱ级	19	341 ± 66	271 ± 47	17	345 ± 74	339 ± 58
Ⅲ级	14	391 ± 74	368 ± 66	12	402 ± 82	395 ± 79
Ⅳ级	8	393 ± 68	376 ± 64	10	398 ± 77	386 ± 78

1)病情分级采用 Kellgren-Lawrence 分级标准

3.3　血清 TNF-α 水平　治疗前 2 组各级别患者血清 TNF-α 水平比较,差异无统计学意义($F = 1.447$,$P = 0.695$)。治疗 12 周后加味青娥丸组患者血清 TNF-α 水平与治疗前相比,差异有统计学意义($F = 103.189$,$P = 0.000$);Ⅰ、Ⅱ级患者血清 TNF-α 水平较治疗前降低($P = 0.000$;$P = 0.000$),Ⅲ、Ⅳ级患者血清 TNF-α 水平与治疗前相比,差异均无统计学意义($P = 0.281$;$P = 0.079$)。治疗 12 周后芍药丸组各级别患者血清 TNF-α 水平与治疗前相比,差异无统计学意义($F = 1.065$,$P = 0.786$)。治疗 12 周后 2 组患者血清 TNF-α 水平比较,差异有统计学意义($F = 13.958$,$P = 0.003$);加味青娥丸组Ⅰ、Ⅱ、Ⅳ级患者血清 TNF-α 水平均低于芍药丸组($P = 0.000$;$P = 0.000$;$P = 0.018$);2 组Ⅲ级患者血清 TNF-α 水平比较,差异无统计学意义($P = 0.125$)。见表 5。

表 5 2 组 KOA 患者血清 TNF - α 水平比较 $\bar{x} \pm s$,pg · mL^{-1}

病情分级1)	加味青娥丸组			芍药丸组		
	例数	治疗前	治疗 12 周后	例数	治疗前	治疗 12 周后
Ⅰ级	19	236 ± 43	153 ± 41	21	235 ± 42	228 ± 38
Ⅱ级	19	241 ± 55	149 ± 43	17	238 ± 52	231 ± 51
Ⅲ级	14	284 ± 54	274 ± 47	12	298 ± 58	288 ± 52
Ⅳ级	8	274 ± 51	258 ± 48	10	288 ± 54	279 ± 48

1)病情分级采用 Kellgren - Lawrence 分级标准

3.4 血清 NO 水平 治疗前 2 组各级别患者血清 NO 水平比较,差异无统计学意义($F = 0.505$,$P = 0.918$)。治疗 12 周后加味青娥丸组患者血清 NO 水平与治疗前相比,差异有统计学意义($F = 25.740$,$P = 0.000$);Ⅰ、Ⅱ级患者血清 NO 水平较治疗前降低($P = 0.000$;$P = 0.000$),Ⅲ、Ⅳ级患者血清 NO 水平与治疗前相比,差异均无统计学意义($P = 0.080$;$P = 0.121$)。治疗 12 周后芍药丸组各级别患者血清 NO 水平与治疗前相比,差异无统计学意义($F = 0.427$,$P = 0.935$)。治疗 12 周后 2 组患者血清 NO 水平比较,差异有统计学意义($F = 5.621$,$P = 0.039$);加味青娥丸组Ⅰ、Ⅱ级患者血清 NO 水平均低于芍药丸组($P = 0.000$;$P = 0.000$);2 组Ⅲ、Ⅳ级患者血清 NO 水平比较,组间差异无统计学意义($P = 0.062$;$P = 0.226$)。见表 6。

表 6 2 组 KOA 患者血清 NO 水平比较 $\bar{x} \pm s$,pg · mL^{-1}

病情分级1)	加味青娥丸组			芍药丸组		
	例数	治疗前	治疗 12 周后	例数	治疗前	治疗 12 周后
Ⅰ级	19	105 ± 12	72 ± 6	21	101 ± 11	98 ± 9
Ⅱ级	19	104 ± 13	76 ± 7	17	108 ± 12	105 ± 10
Ⅲ级	14	148 ± 16	143 ± 15	12	143 ± 15	138 ± 14
Ⅳ级	8	133 ± 15	129 ± 13	10	135 ± 16	132 ± 14

1)病情分级采用 Kellgren - Lawrence 分级标准

3.5 PBMC MMP - 3 mRNA 水平 治疗前及治疗 12 周后,2 组各级别患者 PBMC MMP - 3 mRNA 水平比较,组间差异均无统计学意义($F = 0.002$,$P = 0.999$;$F = 0.033$,$P = 0.998$)。治疗 12 周后加味青娥丸组和芍药丸组各级别患者 MMP - 3 mRNA 水平与治疗前相比,差异均无统计学意义($F = 0.029$,$P = 0.999$;$F = 0.002$,$P = 0.999$)。见表 7。

表 7 2 组 KOA 患者 PBMC MMP - 3 mRNA 水平比较 $\bar{x} \pm s$

病情分级1)	加味青娥丸组			芍药丸组		
	例数	治疗前	治疗 12 周后	例数	治疗前	治疗 12 周后
Ⅰ级	19	0.89 ± 0.34	0.78 ± 0.28	21	0.91 ± 0.32	0.88 ± 0.28
Ⅱ级	19	0.85 ± 0.32	0.79 ± 0.27	17	0.86 ± 0.33	0.87 ± 0.31
Ⅲ级	14	0.79 ± 0.26	0.73 ± 0.23	12	0.81 ± 0.28	0.80 ± 0.29
Ⅳ级	8	0.78 ± 0.32	0.71 ± 0.24	10	0.81 ± 0.31	0.79 ± 0.28

1)病情分级采用 Kellgren - Lawrence 分级标准

4 讨 论

KOA 是各种因素导致关节软骨、软骨细胞外基质和软骨下骨的合成分解代谢异常,从而引起的一种关节疾病[10]。临床表现多为关节局部疼痛、触压痛、关节活动受限、关节肿胀和其他炎症反应引起的相关症状,病理上表现为细胞和细胞外基质发生形态、生物学、分子和生物力学各方面的改变,最终导致了关节软骨的软化、纤维化和丢失,软骨下骨的硬化、软骨下囊形成,以及骨赘形成[11]。很多细胞因子和生长因子在 KOA 的病理进程中调节着软骨、软骨细胞外基质和软骨下骨的合成与分解代谢,如细胞因子、生长因子、聚蛋白酶和 MMP 等都参与了其调控[12-13]。IL - 1β 和 TNF - α 是 OA 病理过程中促进软骨基质降解和关节软骨破坏的最重要的细胞因子[14-15]。另外,降低 NO 的合成量也能抑制软骨细胞调亡和关节软骨的降解退变[16]。

MMP 是导致软骨退变降解的首要因素[17]，MMP－3在软骨基质的降解过程中起关键作用，它能降解软骨蛋白聚糖并裂解核心蛋白，从而导致氨基葡聚糖承载碎片丢失，最终造成关节软骨功能丧失[18]。MMP－3 主要在 OA 患者的滑膜细胞中表达，同时在软骨细胞和单核细胞也有少量表达。在 KOA 与全身 OA 患者的血清中，MMP－3 浓度均较正常组明显升高，因此它在骨关节疾病的诊断与治疗中起着非常重要的作用[19]。

IL－1β 能够促使Ⅱ型胶原合成与强度下降，改变软骨中胶原成分；促进软骨细胞凋亡，改变软骨细胞正常结构与功能；还可促进滑膜炎症发展，滑膜皱壁增生，造成关节软骨生存的恶劣微环境，加速 OA 进展[20]。TNF－α 在 KOA 的发病过程中与 IL－1β 起着协同作用[21]，且与一些疼痛和痛觉过敏的程度有关[22－23]。有研究表明，阻断 TNF－α 可使各种神经病理性疼痛模型大鼠或小鼠的痛觉增敏[24－25]。

关节内 NO 含量增高可抑制软骨细胞增值，加速软骨细胞凋亡。由于炎症，关节局部高浓度细胞因子刺激软骨细胞、滑膜细胞等，使其诱生型一氧化氮表达增强，NO 产生增加[26]。高浓度的 NO 能抑制胶原和蛋白多糖合成[27－28]，降低 IL－1 受体拮抗剂的表达[29]，提高其易受其他氧化剂损害的敏感度[30]，激活 MMP[31－32]，抑制软骨细胞增殖[33]，诱导细胞调亡[34－37]，从而导致关节软骨的功能严重受损。

加味青娥丸是根据中医“肾主骨”原理，在传统补肾中药方青娥丸基础上，加用活血中药丹参，从整体上调理肝肾，强壮筋骨。本试验中，治疗前 2 组患者血清 IL－1β、TNF－α 和 NO 的浓度无差异，且 VAS 及 WOMAC 评分无差异；治疗 12 周后，加味青娥丸组 Kellgren－LawrenceⅠ、Ⅱ级患者 IL－1β、TNF－α 和 NO 的水平明显下降，且 VAS 及 WOMAC 评分也随之下降，提示早期 KOA 患者血液中较高浓度的 IL－1β、TNF－α 和 NO 可能是引起疼痛的主要发病机制之一，加味青娥丸治疗早中期 KOA 的机理之一可能是通过各种途径下调血清 IL－1β、TNF－α 及 NO 水平，从而抑制软骨细胞凋亡和软骨基质降解。至于加味青娥丸是否能影响 KOA 患者关节组织结构，本试验尚不能得出结论，有待更长期和深入的试验及临床研究。

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童应使用直径 3.0 ~ 3.5 mm 的弹性髓内钉;②髓内钉越粗所产生的弹力就越大,固定就越牢靠,但插入的难度也随之增大;③注意防止术后钉尾周围激惹反应的发生[18-20]。

本研究结果显示,与切开复位钢板内固定相比,采用 AO 钛制弹性髓内钉内固定治疗小儿肱骨干中下段骨折,创伤小、手术时间短、骨折愈合快,肩、肘关节活动度及功能恢复好,可作为临床治疗小儿肱骨干中下段骨折的一种较为理想的选择,但二者住院时间无明显差异。

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